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James Reilly and the autonomic nervous system

A prophet unheeded?

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Biographical note

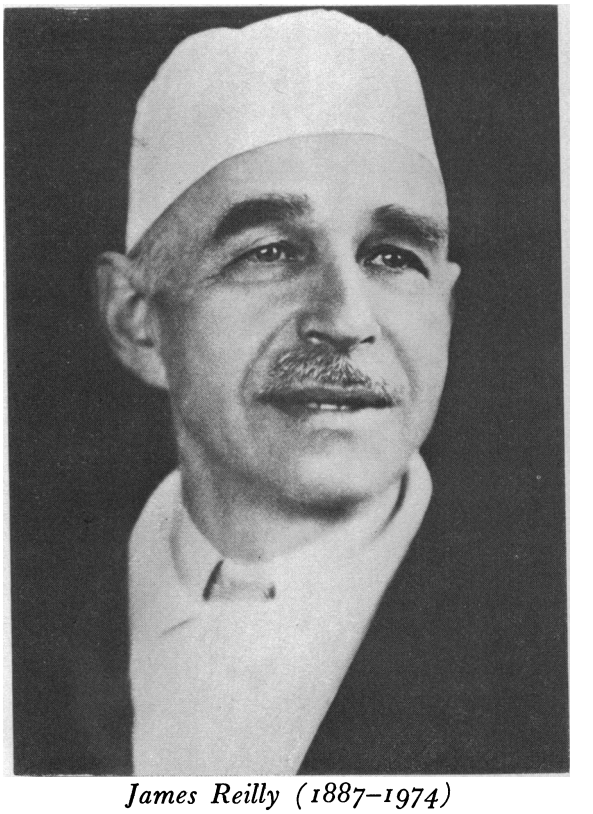
Sometimes modesty and self-effacement, especially in scientific research, can hinder progress as much as over-anxious seeking of publicity can do by making premature claims which subsequently prove false. Certainly this is true of the late Dr James Reilly, who for over 40 years conducted research in Paris into the physiopathological processes of disease with results which, although challenging the basic principles of conventional teaching, remain unknown outside Europe. There are several reasons for this apparent neglect, but most of them can be found in the character of the man himself.

Born in 1887, Reilly was descended from an Irish rebel who, condemned to death, was subsequently pardoned and banished to France. Both his parents died when he was three to four years old and he passed into the care of some rather cold and tight-fisted near relatives. Apparently they never ceased to remind him of his impecunious state so that he became consumed with an obsession about poverty. He lived alone in sparsely furnished rooms in the Rue de Vaugirard in conditions approaching monastic simplicity and travelled across Paris second class in the Métro to reach his hospital. When his friends reproached him and encouraged him to take better care of himself he always replied, 'But you do not understand, I have always been poor'.

Through the generosity of another female relative he was able to study medicine in Paris. After graduation and serving in the French Army during the First World War he had an appointment at the Pasteur Institute, where he designed a method of culturing anaerobic bacteria known to this day as Reilly's tubes. In 1922 he was appointed director of the newly created Central Laboratory of the Claude Bernard Hospital for Fevers in Paris, a position he was to occupy for over 40 years. He died in 1974.

Reilly was a clinician as well as a laboratory worker. He had good powers of observation and the gift of selecting significant features from a confused mass of symptoms presented by a patient. He had an excellent and a selective memory which allowed him to use isolated facts read and remembered many years before. For example, once he was asked where he got his idea that nervous irritation played a part in pathology. In reply he quoted an obscure paper published in a foreign specialised journal in 1894, when he was seven years old.

His method of research was a combination of intuition and deduction. By intuitive processes he would formulate a hypothesis and then prepare a very carefully thought out programme of research with the aim of either confirming and substantiating his hypothesis or showing it to be false. He was an extremely severe critic of his own and other people's work and never accepted questionable findings or made unjustified claims



James Reilly (1887–1974)

As a person Reilly was unpredictable and very difficult to approach. On some days he would appear taciturn and hostile but on others a brilliant and humorously ironic conversationalist, covering a great variety of topics and revealing a wide knowledge of literature (he was a great admirer of James Joyce), music, and the arts in general. He had very few intimate friends but in those he had he inspired the deepest affection.

His avoidance of publicity was almost pathological. He only agreed to be proposed a member of the Académie Nationale de Médecine provided he could dispense with the customary courtesy visits to the other members. In spite of strong persuasion from his friends and colleagues he steadfastly refused to accept a chair in the Collège de France once occupied by Claude Bernard. When some people suggested he should be nominated for a Nobel Prize he strongly opposed such action. It is said that he requested that no acknowledgment of his death should be made until after his funeral.

Apart from a few contributions to the Société de Biologie all his major papers appeared in a much respected journal, the *Annales de médecine*, which was little read outside France and ceased publication soon after the Second World War. He preferred this journal because the editors put no limit to the length of his papers. The disappearance of this periodical and the fact that many of his contributions appeared during the German occupation of France account for the lack of knowledge about his work amongst Anglo-Saxon readers.

The Reilly phenomena

Certain clinical and experimental observations had convinced Reilly that the autonomic nervous system was far more closely concerned in infectious diseases than had hitherto been thought. To test this hypothesis he devised in 1932[1] a highly original experimental technique which consisted in applying a stimulus to a segment of the peripheral sympathetic nervous system (for example, the splanchnic nerve or coeliac ganglion) either by depositing on it a bacterial toxin or a chemical irritant substance or by physical means such as faradisation. He applied this technique to a variety of animals (rats, guineapigs, rabbits, dogs, cats, monkeys), exploring all the main visceral territories. Over the course of time he improved the conditions of his experiments and as they developed the wide extent of their potential field of application became more and more evident. Briefly, the acute results of irritation of abdominal sympathetic nerves appeared as an intense vasomotor reaction visible as gastrointestinal haemorrhage and proliferation of lymphoid tissue.

It is impossible to condense the work of 40 years into a short paper. The best one can achieve is to indicate the general lines of investigation which he undertook. These can broadly be divided into three sections—the part played by the autonomic nervous system in (1) inflammatory processes and immunity; (2) the physiopathology of infectious diseases, especially typhoid fever; and (3) other pathological processes.

1) INFLAMMATORY PROCESSES AND IMMUNITY

Inflammation The autonomic nervous system is concerned in two aspects of tissue inflammation: (1) vasomotor and (2) reticuloendothelial.

The experimental protocol briefly outlined above (that is, irritation of peripheral sympathetic nerves) results in an intense vasomotor reaction in the digestive tract evidenced by vasodilatation and hyperaemia together with an increase of capillary permeability with serous or haemorrhagic exudate. Within a few hours the reticuloendothelial system begins to participate, as evidenced by swelling of endothelial cells with enhanced ingestive capacity, seen particularly in the Kupffer cells of the liver. The reticular cells of the spleen and the lymphoid formations of the intestinal tract undergo hyperplasia, eventually being transformed into macrophages with, in places, syncytial formation.

All these changes suggest that the tonicity and the vitality of the reticuloendothelial tissues are to a large extent dependent on reflexly induced activity in the autonomic nervous system.

Immunity Inflammation also affects the processes of immunity. The autonomic nervous system, through its influence on the progress of infection, is concerned in local defence mechanisms. It has long been known that vasodilatation contributes to immunity by promoting diapedesis of leucocytes. Reilly's experiments proved that the autonomic nervous system also acts by increasing the phagocytic properties of reticuloendothelial tissue.

A process devised by Reilly known as the 'sac jugulaire'[2] demonstrates this particular point and several other aspects of the effects of autonomic irritation. A segment of rabbit's jugular vein is tied off at both ends. When a

chemical or bacterial irritant is placed in this segment the effects of irritation are evident not only locally but also elsewhere in the body, taking the form firstly of albuminuria and subsequently of congestion and gastrointestinal haemorrhage. Reilly's observations of the effects of a lycopodium emulsion when placed in such a sac are noteworthy. After a week histological examination of the carotid artery showed diffuse swelling of the vascular endothelium due to stimulation of the sensory sympathetic fibres of the blood vessel. A week later a streptococcal culture which previously had without fail produced a fatal septicaemia in control animals was injected intravenously. All the prepared animals survived. Some ran a mild temperature and some developed monoarthritis, but in none did a positive blood culture occur. The conclusion from this experiment was that prolonged stimulation of the sensory nerve fibres of the walls of blood vessels can, through a reflex mechanism, confer some degree of immunity and arrest infection.

A similar finding followed irritation of lymphoid structures. Reilly found that inoculation of typhoid or paratyphoid bacilli into the mesenteric lymph nodes of rabbits or guineapigs invariably led to death from septicaemia[3]. Although this was not prevented by previous vaccination, it was prevented by moderate faradisation of the splanchnic nerve half an hour before the inoculation[4]. Histological examination of the mesenteric lymph nodes revealed the protective mechanism. In the control animals no appreciable histological changes were noted during the first few days. In the faradised animals, on the other hand, gross structural changes were seen in lymph nodes in less than 24 hours, taking the form of congestion, vasodilatation, exudation of fibrin, hyperplasia of reticular cells, and an increase of polymorphonuclear cells followed by the appearance of necrotic foci and finally sclerosis. Thus the autonomic stimulation had led to lymphoid reaction which prevented the multiplication and spread of bacteria and the release of endotoxin, so that the disease was in fact limited to a lymphoid infection.

It is worth noting, however, that if the experimental procedure was changed and intense rather than mild faradisation applied, diffusion of bacteria was paradoxically increased and ultimately led to death from septicaemia.

2) TYPHOID FEVER AND OTHER INFECTIOUS DISEASES

Systemic manifestations In the course of his work at the Claude Bernard Hospital in Paris Reilly had to undertake the postmortem examination of patients dying of typhoid fever. His early work on the effects of autonomic irritation, combined with his observations of the constant finding of enlarged lymph nodes in the mesentery, led him to build up the following hypothesis: Typhoid fever follows the ingestion of typhoid bacilli which, instead of setting up inflammation in the wall of the intestine, immediately move through it to reach the mesenteric lymph nodes, where they multiply during the incubation period, being responsible for an essential morbid characteristic of the disease—swelling of the mesenteric lymph nodes. The appearance of clinical symptoms coincides with (1) systemic spread of the bacilli evidenced by positive blood culture and (2) lysis of the bacilli in situ with release of endotoxin.

Reilly confirmed this thesis by producing typhoid fever in animals after placing living bacilli in the lymph nodes of the mesentery[3]. He was the first person to do this. His technique reproduced all the main clinical and pathological features of the human disease—that is, an incubation period followed by fever, diarrhoea, prostration, positive blood culture, and a positive agglutination test. Autopsy showed congestive or haemorrhagic swelling of the mesenteric lymph nodes and swelling, haemorrhagic congestion, and necrosis of Peyer's lymphoid patches in the small intestine.

He next proceeded to establish that these pathological changes were the result not of any action of the living bacilli but of the endotoxin liberated by dead organisms. Exactly the same changes occurred after the inoculation of endotoxin into the heart or lymph nodes of a guineapig.

These observations convinced Reilly that endotoxin released in the mesenteric lymph nodes had a selective affinity for sympathetic nervous tissue. To test this idea he injected a very small quantity of typhoid antigen close to the splanchnic nerve or coeliac ganglion of

a guineapig. The effect was dramatic: intestinal lesions typical of typhoid followed a very small dose which was harmless when administered elsewhere. These changes were not confined to guineapigs but occurred in a variety of animals[4].

In a final series of experiments he found that these lesions were not in fact specific to the typhoid endotoxin itself but that they followed any irritation of the sympathetic nervous system. They could be reproduced by depositing around the splanchnic nerve very small quantities of various irritant substances such as diphtheritic toxin (0.005 ml in guineapigs), 20% ethanol, salts of lead, nickel, or cobalt, oil of chloroform, various alkaloid substances such as nicotine or chelidonium extract, and so on. The same effects were also obtained by purely physical means such as faradisation for 30 seconds, ligation with a linen thread, or irritation with a sterile rose thorn[1].

To sum up, the above-mentioned findings led to the idea that the pathological changes of typhoid fever are the result of a two-fold affinity, that of bacilli for lymph nodes and that of endotoxin for sympathetic nerve endings. Furthermore, the susceptibility of sympathetic nervous tissue to irritation is evidenced by the production of identical pathological changes by a wide variety of substances which have a common property—that of irritation. Thus the irritation of nervous tissue is responsible for the lesions of the lymphoid tissue; the effects of typhoid endotoxin are due only to its affinity for sympathetic nerves.

Gastrointestinal haemorrhage It is not difficult to produce gastrointestinal haemorrhage in experimental animals by depositing typhoid endotoxin on abdominal sympathetic nerves, as one of us (RL) has done many times. The same result is obtained with many other substances. Therefore the mechanism of the intestinal haemorrhages of typhoid fever is the same as that of the lymphoid lesions.

The microscopic picture shows the same lymphoid lesions—congestion amounting in some instances to infarction—and in the vascular system degenerative or proliferative endotheliitis. Probably the vasodilatation is the result of anoxic anoxia secondary to vasoconstriction, while the subsequent endothelial changes are probably the result of histotoxic or stagnant anoxia leading to local release of active but harmful biochemical substances.

Central nervous involvement A relationship between injury to autonomic centres in the diencephalon and gastrointestinal haemorrhage has been known for over a century. Gastrointestinal haemorrhage is also a terminal feature not only of typhoid fever but of severe Gram-negative infections in general. The mental torpor accompanying severe typhoid fever also suggests an action by endotoxin on the central nervous system, particularly of the diencephalon. Professor Guy Tardieu demonstrated such an effect 30 years ago in Reilly's laboratory[5]. He introduced a very small quantity, as little as 0.001 mg, of typhoid antigen into the third ventricle of a dog by means of a puncture of the lateral ventricle. To use his own words, 'This immediately plunged the animal into a catatonic state'. This condition, due to deep torpor, lasted for several days, during which time the animal became febrile, had looseness of the bowels, and lost weight. Larger doses induced cardiovascular collapse and intestinal haemorrhage. To obtain the same effect by a systemic administration it would be necessary to use a dose at least 200 times greater.

This experiment surely makes it clear that one of the most remarkable attributes of the endotoxin of typhoid fever is its affinity for peripheral and central sympathetic nervous tissue. Indeed, this is a common property of all the endotoxins produced by Gram-negative organisms.

Scarlet fever Reilly's previous work on scarlet fever led him to believe that this disease would offer an interesting field of investigation. The Dick toxin extracted from the haemolytic streptococci responsible for scarlet fever is not harmful when injected subcutaneously or intravenously, but if a very small amount comes into contact with any part of the sympathetic nervous system of an experimental animal it immediately has rigors, albuminuria (sometimes with blood), increased blood urea concentration, congestion and at times purpura of the abdominal wall, and cardiovascular collapse indistinguishable from bacteraemic shock and culminating in death. Postmortem

examination reveals lesions identical with those of malignant scarlet fever: congestion and purpura of the abdominal wall and of the peritoneum, haemorrhagic suffusion of the viscera, congestion and haemorrhages in the glomeruli of the kidneys, and swelling of Peyer's patches and the lymph nodes of the mesentery. This same property of neurotropism shown by bacterial exo- and endotoxins is possibly at work in other infectious diseases—for example, exanthematous typhus and whooping cough, the toxin of which in the dog has the same effect as typhoid endotoxin.

Although the experiments summarised so far have dealt only with infectious pathology, they show that disorders caused by irritation of the sympathetic nervous system are not specific for any particular agent.

Relation to human infectious diseases After the publication of the work of Reilly and his colleagues on autonomic irritation in animals Marquezy and Ladet, who worked at the Claude Bernard Hospital, published an account of the autopsy findings of some 90 patients dying in the hospital from what in Britain would be called 'overwhelming infection' and which the French refer to as 'le syndrome malin des maladies infectieuses'[6]. Although the pathophysiology of this syndrome is today regarded as very complex and involving many factors, there was indeed a striking similarity between the macroscopic and microscopic findings of the human diseases and those produced experimentally by Reilly and his colleagues. We may infer that irritation of various segments of the peripheral and central nervous system plays an important role in 'overwhelming infections'. This could be regarded as a generalised Reilly's phenomenon.

3) OTHER PATHOLOGICAL PROCESSES

Nephritis Since previous experiments had shown that extensive damage to the endothelium of the vascular system could follow irritation one would expect that the glomerulus of the kidney, with its very special capillary structure, should be particularly susceptible to this kind of stress. Once again Reilly submitted his hypothesis to experimental proof[7]. The deposition of a minimal quantity of typhoid, cholera, or streptococcal toxin on the splanchnic nerve or the renal plexus of guineapigs, rabbits, cats, or dogs produced albuminuria, haematuria, casts in the urine, a raised blood urea concentration, oliguria, and sometimes anuria. Microscopic examination of the kidneys post mortem showed renal congestion, swelling of glomerular loops, and exudation of albumin or blood into the glomerular tufts. That these changes were neurogenic in origin was shown by the suppression of the effect if the procedure was preceded by denervation of the kidney. Even irritation of sympathetic nerves at some distance from the kidney evoked a renal response. For example, such a response to stimulation of the stellate ganglion brings to mind the connection between pharyngeal infections and glomerulonephritis. Also injection into the mucous membrane of the pharynx of various irritant substances (human serum, powdered ipecacuanha, colloidal silica, 5% peptone) produced albumin and blood in the urine of guineapigs and rabbits, whereas if preceded by painting the pharynx with cocaine no such changes took place.

Experimental subacute nephritis[8] Prolonged irritation of sympathetic nerves can also produce changes identical with those of subacute glomerulonephritis. Sixty cats received an injection of 0.033 ml of an emulsion of silica particles under the tunica adventitia of the renal artery. In the following weeks 25% of these animals had albumin in their urine, an increase in their blood urea concentration, and hypertension. In 2 or 3 months diffuse subacute glomerular lesions developed, with oedema, hyalinisation, and proliferation of endothelial cells in the glomeruli. The mechanism of this type of experimental nephritis is different from that of Goldblatt nephritis. There was no reduction in the calibre of the lumen of the renal artery and the renal lesions were confined to the glomeruli. Furthermore, injections of silica particles into the aorticorenal lymph nodes—that is, at some distance from the renal artery—also produced identical diffuse glomerulonephritis in 10 of 25 cats.

Present-day explanations for glomerulonephritis run in quite a different direction and one might therefore suppose that nothing can be derived from Reilly's experiments concerning human renal pathology. This may be true at present, but Reilly also pointed out with some truth that during the Second World

War there were many thousands of wounded soldiers in France with wounds infected with haemolytic streptococci, yet none of them apparently developed nephritis. There can be no doubt about the strict scientific accuracy and the objectivity with which Reilly conducted his experiments and one can expect that one day they may find their own place in an enlarged concept of the physiopathology of glomerulonephritis.

Intussusception Intestinal intussusception, sometimes 10 cm in length, can be produced in the guineapig by irritation of the splanchnic nerve. The connecting link between the sympathetic nervous system and the intestine may be the mesenteric lymph nodes, since the lesion can be produced by the injection into the ileocaecal lymph node of various endotoxins, of poisons such as ricin, or, in a sensitised animal, of an allergen such as trichophytin.

Such experimental intussusception is comparable to that sometimes encountered in small children suffering from mesenteric lymphadenitis. Reilly[9] made an extract from the mesenteric nodes of children with intussusception and injected a small quantity (0.1 ml) into the mesenteric nodes of 40 guineapigs. Fourteen per cent of the animals developed an intussusception, although injection of various other irritant substances into the mesenteric nodes of 100 control animals was without effect. This suggests that intussusception in mesenteric lymphadenitis is due to a specific property of the agent.

Effects of irritation of arterial adventitia One of us (RL), working in Reilly's laboratory, studied the reactivity of the sympathetic nerve endings of the tunica adventitia of arteries to irritation.

1) A group of 102 rabbits received 0.2 or 0.3 ml of an irritant under the adventitia of the femoral artery. In 50% hyperplasia of the endothelium of the artery or even obstruction of the lumen, with or without thrombosis, occurred. Unilateral section of the lumbar sympathetic nerves to the artery following irritation of both arteries prevented the lesion on the side where the nerve was cut[10].

2) Injection of various irritant substances (trypan blue, cantharides, mustard, or 1/400 or 1/500 croton oil) under the aortic adventitia of 16 rabbits and 36 dogs produced changes in the repolarisation of the electrocardiogram in 13 of the animals. In 6 animals the anomalies were those associated with anterior myocardial infarction. Postmortem examination of the myocardium of these animals revealed oedema, extravasation of blood, and degenerative myocardial lesions proceeding in some cases to necrosis. In one case an infarct was visible macroscopically. Thus true myocardial infarction can arise through a purely reflex mechanism[11].

Experimental research was but a part of Reilly's extensive work, but this paper has tried to confine itself to experimental techniques and conclusive data. His research was remarkable for its continuity and its unity. The technique was simple but absolutely original. In brief it consisted in the irritation of any sympathetic structure by means of substances like microbial toxins, chemical poisons, and mineral salts as well by purely physical means such as faradisation. Whatever the area involved the local damage is always strikingly similar, associating various degrees of vasomotor disorder.

He tried to cast new light on the basis of human pathology through a simple experimental technique which he devised himself. His colleagues in France have acknowledged his discovery by giving his results the title 'Le syndrome d'irritation neuro-vegetative de Reilly'.

COMMENT

Reilly's phenomena may be considered to be essentially the same as those described by Selye as resulting from 'acute stress'—part of his 'general adaptation syndrome', the description of which was published 6 years after Reilly's original papers. Selye's 'stressor' agents were similar to Reilly's irritant substances, but he used them in greater quantities and did not regard the autonomic nervous system as important.

Reilly's research, conducted with remarkable dedication for over 40 years, surely established the importance of the sympathetic nervous system in the production of these changes, basically vasomotor in origin and all,

irrespective of the causal agent, sufficiently similar to justify the term 'non-specific'. Although he agreed that the endocrine and reticuloendothelial systems were involved, he considered that vasoconstriction was the initiating factor of the effect that followed, whether acute or chronic. Beyond this he could not go, nor could he contemplate embarking upon projects aimed at the elucidation of the causal mechanisms with the limited facilities at his disposal.

Paul Dell, the French neurophysiologist, many years ago expressed the opinion that the brainstem reticular formation played some part but felt that knowledge of the physiology, pharmacology, and detailed organisation of this part of the brain was too limited at that time to permit the formulation of any hypothesis[12]. During the past 10 years, however, Scandinavian research workers, by means of histochemical fluorescence techniques, have demonstrated the presence of noradrenergic neuronal pathways in the central nervous system[13]. Groups of noradrenergic neurones in the pontomedullary reticular formation have been shown to send axons upwards to the hypothalamus via the posterior longitudinal bundle as well as downwards to the sympathetic outflow in the lateral columns of the spinal cord. During the same period there have also been additions to knowledge of afferent visceral nervous connections with the central nervous system[14]. These have been shown to have a widespread distribution, the hypothalamus and limbic system (McClean's 'visceral brain') receiving a particularly rich supply. Recent electron microscopic studies have also added to knowledge of the neuronal cell bodies in the sympathetic ganglia and their terminal fibres[15]. The terminal fibres expand into what are called 'terminal varicosities', which have a noradrenaline content 3000 times greater than that found in the cell body. Significantly, the terminal varicosities occur in greatest profusion amongst the smooth muscle fibres of the smallest arterioles, conferring on them an immense contractile capacity which one authority has described as 'sphincteric' in nature.

Thus it is entirely credible to suggest that strong visceral afferent nervous stimulation can bring about reflex noradrenergic activity resulting in profound vasoconstriction, intensified by simultaneous hypothalamic excitation releasing pitressin from the posterior pituitary which in its turn brings about release of angiotensin I and its conversion into angiotensin II.

The search for a pharmacological antagonist to the Reilly phenomena

Since 1935 extensive but, at first, unsuccessful attempts to prevent or reverse the Reilly phenomena have been undertaken with substances which have included adrenolytic compounds, ganglion-blocking agents, pituitary extracts, procaine, and atropine[16]. The suggestion that histamine release through an axon reflex was the cause[17] led to the synthesis of antihistamine compounds, which in their turn also proved quite ineffective[18]. Fortunately, the continued interest of the French pharmaceutical industry in this problem led them to the further study of aminated compounds of phenothiazine after failure to demonstrate hoped-for trypanocidal properties in such compounds had led to their abandonment by the American industry[19]. The new products were found to have a central depressant action on autonomic reflex activity and hence possibly on the phenomena. Although some of the early compounds (promethazine and diethazine) appeared to have little effect, a later compound, chloropromazine, was found to exert positive protection. Reilly demonstrated protection of guineapigs against the irritant effects of typhoid antigen, converting a 90% mortality in control animals into a 70% survival in animals protected by chloropromazine in a concentration of 2 mg/kg body weight given by continuous subcutaneous injection[20, 21]. Tardieu, one of Reilly's assistants, also using chlorpromazine, prolonged survival from a few hours to more than 24 (with one recovery) in dogs subjected to central irritation of the medullary reticular formation by injection of croton oil, a procedure with hitherto 100% mortality[22].

Apart from a suggestion by Reilly that chlorpromazine could be useful in treatment of typhoid fever these results evoked little interest, for two reasons. Firstly, chlorpromazine was one of the constituents of a mixture of drugs employed to produce a condition called

'artificial hibernation' which, it was asserted, reduced shock and morbidity following major surgery on elderly 'poor-risk' patients. The claims were not substantiated and the method was discredited and rejected, as was the use of chlorpromazine generally in anaesthesia and surgery in spite of attempts by Tardieu[23, 24] and one of us (DABH)[25] in the French and British medical press to emphasise that chlorpromazine was the only active constituent and that better results would have followed its use alone.

Secondly, the introduction of chlorpromazine into psychiatry for the treatment of schizophrenia was followed by immediate clinical and commercial success. From that moment all research into its mode of action became confined to centres of psychiatric and neurophysiological research, which only published their findings in highly specialised journals or at equally highly specialised international symposia. Thus the demonstration by Bradley that chlorpromazine reduced the intensity of responses in the brainstem reticular formation to external stimuli[26] and also that it did so by antagonising the central excitatory effects of noradrenaline[27] escaped notice, although these actions offer a satisfactory explanation for its wide spectrum of activity (its trade name, Largactil, being devised to suggest 'large action'), in particular its protective action against autonomic irritation and most forms of shock.

Clinical significance of the phenomena

If the Reilly phenomena are accepted as a model for the tissue changes taking place in toxaemia of every kind (including those of bacterial origin), then the idea that toxins have a direct destructive action on individual cells needs revision. Reilly's experiments demonstrate clearly that toxins bring about tissue changes reflexly through an irritant action on sympathetic nervous tissues, for which they have a special affinity. Thus changes occurring in the central nervous system initiate vasomotor, endocrine, and reticuloendothelial activity evident peripherally as the phenomena, which are non-specific although varying in intensity. Vasomotor responses predominate, causing persistent anoxia, first anoxic then histotoxic, proceeding ultimately to stagnant anoxia, a process comparable to the 'circulatory decay' of Lillehei. The resemblance to the pathological findings in irreversible shock is more than coincidence, and in France this is widely accepted. If one thinks not so much of 'shock' but of 'response to injury' the two states merge more easily. The concept of a primary involvement of the central nervous system in the evolution of all non-specific changes occurring after injury (including bacterial) offers an opportunity to narrow the target for therapeutic measures and encourage a search for ways and means of control by modification or regulation of impulses *entering* the brain rather than, as in the past, by attempting to block *outgoing* impulses at the periphery.

Reilly was not the first to emphasise the importance of the central nervous system in the development of pathological states and alterations in immunity. Speransky in Russia came to similar conclusions some years earlier, although Reilly, together with other Western research workers, remained in ignorance of this until 1942, when an English translation of the work was published[28].

Reilly's experiments give good grounds for belief that conditions like acute dilatation of the stomach, gastric haemorrhage, acute intussusception, and acute pancreatitis are the result of autonomic irritation and therefore that, in clinical practice, operative trauma and infection could well be contributory factors to such complications.

A feature of autonomic irritation most immediately relevant to present-day clinical medicine is undoubtedly the changes in renal function which result. In his monograph on experimental nephritis Reilly observed that the most consistent sequel of autonomic irritation is the production of albuminuria and haematuria to an extent that often compromises research projects undertaken with other objects in view. Albuminuria was a regular sequel of irritation set up in the isolated 'sac jugulaire' experiment, so there can be no doubt that it arises from a reflex of central origin or that the cause is vasoconstriction, as it must be also in the depression of renal function after trauma, haemorrhage, or bacterial shock. The capacity of Gram-negative endotoxin to depress renal function through its central sym-

pathetic stimulant action should be more widely known. Reduction of urinary output sometimes follows vigorous antibiotic therapy for Gram-negative bacteraemia which has resulted in an afebrile patient and a negative blood culture. 'Nephrotoxicity' of the antibiotic concerned is widely accepted as the cause, but the action of Gram-negative endotoxin released from the bacteria which the antibiotic has so successfully destroyed is a more likely explanation. Recent work on the hepatorenal syndrome has revealed that blood endotoxin levels calculated by limulus assay bear a direct relationship to the onset and severity of renal failure[29], and it has also been suggested that 'some other factor' in addition to endotoxaemia 'probably *related to the sympathetic nervous system*' (our italics) may be of importance[30].

If this explanation is correct it would justify an attempt to exploit the protective action of chlorpromazine against the effects of endotoxin by its simultaneous administration with antibiotics, just as Reilly did when protecting animals against typhoid endotoxin released by the action of chloramphenicol on previously inoculated bacilli[21].

As time passes additions to knowledge of central nervous mechanisms for homoeostasis involving the endocrine and autonomic systems bring us nearer to the elucidation of a physiological basis for the Reilly phenomena. Certainly nothing has emerged during the past 25 years to discredit his findings and a great deal which supports them has appeared.

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